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Editorial Comment

The Long QT Syndrome: A G or Not a G?*

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Molecular basis for the long QT syndrome. In the preceding article in this issue of the Journal, Vincent (1) proposes a hypothesis to account for the electropathology of the Romano-Ward variant of the long QT syndrome. Two critical and recent advances in molecular cardiology form the basis for this brief but timely review of an electrophysiologic disease that results in sudden death in the absence of obvious muscle abnormality. First, Keating et al. (2) at the University of Utah have mapped the long QT syndrome locus to the Harvey *ras*-1 gene in seven families. The latter is located on the long arm of chromosome 11 and the protein product of the gene is a guanine nucleotide binding protein (3). Guanine nucleotide binding proteins, also called G proteins, are factors that couple various hormone receptors and effectors, such as adenylyl cyclase, phospholipase C and ion channels (4). The second advance was the observation that both G proteins (G_k) and *ras* proteins (p21 *ras*) modulate acetylcholine-activated potassium ion (K^+) channels in atrial cells (5,6).

Taken alone, neither the work of Keating et al. (2) nor the demonstration of G protein regulation of a K^+ channel pinpoints the molecular basis for the long QT syndrome. Moreover, the absence of linkage to Harvey *ras*-1 in four families and the existence of at least two additional forms of long QT syndrome (the sporadic form and the Jervell-Lange-Nielsen syndrome) make it likely that the underlying genetic abnormalities are heterogeneous. Finally, early speculators have placed their bets on the i_k (delayed rectifier) channel and not the acetylcholine-activated K^+ channel because the latter is probably not the major determinant of repolarization in human ventricular muscle. So why all the excitement?

The Romano-Ward syndrome. As a disease entity, the Romano-Ward syndrome has been well described and, from a physiologic perspective, well characterized. Some of the more obvious features such as sudden death associated with emotional or physical stress, presence of afterdepolarizations and bradycardia at rest were noted long before there was hope of defining specific molecular mechanisms (7). The implication of K^+ channel involvement derives largely from the demonstration that various pharmacologic agents and cations such as cesium (Cs^+) that decrease K^+ conductance also can produce an acquired long QT syndrome. In particular, Cs^+ elicits many of the electrophysiologic abnormalities of the long QT syndrome, including afterdepolarizations and ventricular arrhythmias such as torsade de pointes (8). Of course, an obvious feature of the disease is a strong dependency of arrhythmia on autonomic stimulation (7,9). Although it is not clear whether alpha- or beta-adrenergic receptor activation alone or in concert is required to produce the abnormalities, left-sided autonomic denervation seems to improve survival in affected persons (10).

In short, there is convincing, although circumstantial, evidence pointing to a problem in autonomic regulation of K^+ conductance in myocardial cells. Pinpointing a single protein or family of related proteins underlying this seemingly logical but complex electrophysiology may provide the paradigm needed to unlock the molecular basis of many arrhythmias (9). This is certainly worth getting excited about!

Role of G proteins. But why G proteins instead of an errant K^+ channel? Vincent (1) points to bradycardia at rest as evidence for abnormalities in I_f (the pacemaker channel) function. In addition, the studies of Yatani et al. (11) have established a role for G proteins in the regulation of this channel. Because there is no evidence for generalized autonomic receptor dysfunction in the Romano-Ward long QT syndrome, and mutations affecting two ion channels simultaneously are unlikely, a logical avenue for further investigation would seem to be a signal transduction system that regulates more than one type of channel.

Once this conclusion is reached, the situation gets a bit fuzzy because of insufficient data. Certainly, the multiplicity of genes encoding unique alpha subunits of the G proteins offers an opportunity both for diverse regulation and for potentially numerous genetic mutations (12). In addition, the beta-gamma subunit complex of G proteins has been shown to modulate certain K^+ channels (13). Furthermore, the G proteins are subject to regulation both by other proteins and by post-translational modifications (that is, phosphorylation). Quite possibly, abnormalities in these "extrinsic" modulators could account for defective G protein functions. Finally, it is possible that the small guanine nucleotide binding proteins (H-*ras*-1 or p21-*ras*, for example) are involved in myocardial ion channel regulation as they are structurally and functionally related to the alpha subunits of the G proteins. Thus, even if a defective G protein underlies the problem, work remains to be done to define the mechanism of the dysfunction.

Implications. Although a great deal more information will be forthcoming in the future regarding the diversity, regulation and genetic polymorphisms of myocardial G proteins

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and K^+ channels, it is the Keating group (2) that has paved the way for unveiling the molecular pathology of the Romano-Ward syndrome. Reverse genetics—working backward from deoxyribonucleic acid (DNA) to the protein—has proved to be a powerful tool for getting at the basis of several diseases, such as Duchenne muscular dystrophy (14). If Harvey *ras*-1 is not the abnormal gene, but lies only in close proximity, refined linkage and physical mapping of chromosome 11 should better demarcate the affected region of DNA. Ultimately, sequence comparisons of abnormal and normal segments of DNA and translation of the latter into protein will yield an answer.

In the recent past, speculations on the molecular basis of disease have been confirmed by DNA cloning. For example, physiologic and biochemical studies (15,16) pointed to a chloride channel abnormality in cystic fibrosis that was subsequently demonstrated by identification and cloning of the defective gene. The hypothesis advanced by Vincent (1) synthesizes existing knowledge about the long QT syndrome and in so doing builds an argument that the defect lies in signal transduction at the level of the G proteins. Naturally, we will anxiously await the outcome of the genetic studies. Is it a G or not a G? That, according to Vincent (1), is the question.

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